We Claim:

1. A method of obtaining a representation of the three dimensional structure of a crystal of cytochrome P450 3A4, which method comprises providing the data of at least columns 1, 2, 3, 6 and 7 of Table 3 and constructing an electron density map of said data.

2. The method of claim 1 wherein said map is constructed by reference to the data of column 8 of said Table.

3. The method of claim 1 wherein an initial model of 3A4 is fitted to said map.

4. The method of claim 3 wherein said initial model is refined by reference to the data of columns 4 and 5 of Table 3.

5. The method of claim 1 which further comprises calculating the three-dimensional coordinates of one or more atoms of 3A4 in said crystal to provide a first three dimensional structure of 3A4.

6. The method of claim 5 wherein the structure is that of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å.

7. The method of claim 5 wherein the positions of one or more atoms in said first structure is varied to provide a second structure with three-dimensional coordinates having a r.m.s.d of less than 1.5 Å from said first structure.

8. A computer-based method for the analysis of the interaction of a molecular structure with a P450 structure, which comprises:

providing the P450 structure obtainable by the method of claim 5 or selected coordinates thereof;

providing a molecular structure to be fitted to said P450 structure or selected coordinates thereof; and

fitting the molecular structure to said P450 structure.

9. The method of claim 8 wherein said selected coordinates include atoms from one or more of the residues of Phe57, Phe108, Phe213, Phe215, Phe219, Phe220, Phe241 and Phe304.

10. The method of claim 8 wherein said selected coordinates include atoms from one or more of the residues identified in Table 7.

11. The method of claim 8 wherein said selected coordinates include atoms from one or more of the residues identified in Table 8.

12. The method of claim 8 which further comprises the steps of:

obtaining or synthesising a compound which has said molecular structure; and

contacting said compound with P450 protein to determine the ability of said compound to interact with the P450.

13. The method of claim 8 which further comprises the steps of:

obtaining or synthesising a compound which has said molecular structure;

forming a complex of a 3A4 P450 protein and said compound; and

analysing said complex by X-ray crystallography to determine the ability of said compound to interact with the P450.

14. The method of claim 8 which further comprises the steps of:

obtaining or synthesising a compound which has said molecular structure; and

determining or predicting how said compound is metabolised by said P450 structure; and

modifying the compound structure so as to alter the interaction between it and the P450.

15. A compound having the modified structure identified using the method of claim 14.

16. A method of obtaining an electron density map of a target P450 protein of unknown structure, the method comprises the steps of:

providing a crystal of said target P450;

obtaining an X-ray diffraction pattern of said crystal,

calculating an electron density map of said crystal by reference to the structure factor phase data of Table 3.

17. The method of claim 16 which further comprises modelling the structure of said target P450 of unknown structure on the 3A4 P450 structure obtainable by the method of claim 5 or the structure of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å or selected coordinates thereof ; and

determining a conformation for said target P450 of unknown structure.

18. The method of claim 17 wherein said target P450 protein is selected from the group consisting of 3A5, 3A7 and 3A43.

19. A method for determining whether a compound is bound to P450 3A4 protein, said method comprising:

providing a crystal of said P450 protein;

soaking the crystal with the compound to form a complex; and

determining an electron density map of the complex by employing the data of Table 3 or a portion thereof.

20. The method of claim 19 which further comprises determining the structure of said compound.

21. The method of claim 19 which further comprises the steps of:

obtaining or synthesising the compound; and

modifying the compound structure so as to alter the interaction between it and the P450.

22. A method of determining an electron density map of a target protein which is, or is homologous to, 3A4, which method comprises providing a crystal of the target protein, obtaining an X-ray diffraction of said protein, and generating an electron density map of said target protein by reference to the structure factor phase data of Table 3.

23. A computer-based method for the analysis of the interaction of a molecular structure with a P450 structure, which comprises:

providing a structure comprising a three-dimensional representation of P450 3A4 or a portion of P450 3A4, which representation comprises all or a portion of the coordinates of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å;

providing a molecular structure to be fitted to said P450 3A4 structure or selected coordinates thereof; and

fitting the molecular structure to said P450 3A4 structure.

24. The method of claim 23 wherein said representation further comprises all or a portion of the coordinates of Table 6.

25. The method of claim 23 wherein said selected coordinates include atoms from one or more of the residues of Phe57, Phe108, Phe213, Phe215, Phe219, Phe220, Phe241 and Phe304.

26. The method of claim 23 wherein said selected coordinates include atoms from one or more of the residues of Table 7.

27. The method of claim 26 where said selected coordinates include atoms from one or more of the residues of Table 8.

28. The method of claim 23 which further comprises the steps of:

obtaining or synthesising a compound which has said molecular structure; and

contacting said compound with P450 protein to determine the ability of said compound to interact with the P450.

29. The method of claim 23 which further comprises the steps of:

obtaining or synthesising a compound which has said molecular structure;

forming a complex of a 3A4 P450 protein and said compound; and

analysing said complex by X-ray crystallography to determine the ability of said compound to interact with the P450.

30. The method of claim 23 which further comprises the steps of:

obtaining or synthesising a compound which has said molecular structure; and

determining or predicting how said compound is metabolised by said P450 structure; and

modifying the compound structure so as to alter the interaction between it and the P450.

31. A compound having the modified structure identified using the method of claim 30.

32. The method of claim 23 wherein the molecular structure to be fitted is in the form of a model of a pharmacophore.

33. The method of claim 23 wherein the three-dimensional representation is a model constructed from all or a portion of the coordinates of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å.

34. The method of claim 33 wherein the model is: (a) a wire-frame model; (b) a chicken-wire model; (c) a ball-and-stick model; (d) a space-filling model; (e) a stick-model; (f) a ribbon model; (g) a snake model; (h) an arrow and cylinder model; (i) an electron density map; (j) a molecular surface model.

35. A computer-based method for the analysis of molecular structures which comprises:

(a) providing the coordinates of at least two atoms of a P450 3A4 structure as defined in Table 5 ± a root mean square deviation from the Cα atoms of less than 1.5 Å ("selected coordinates");

(b) providing the structure of a molecular structure to be fitted to the selected coordinates; and

(c) fitting the structure to the selected coordinates of the P450 3A4 structure.

36. The method of claim 35 wherein the selected coordinates are of at least 5, 10, 50, 100, 500 or 1000 atoms.

37. The method of claim 35 wherein the coordinates of Table 5 represent at least a portion of a binding pocket.

38. The method of claim 35 wherein the coordinates of Table 5 comprise at least 2 atoms of the amino acid residues of Table 7.

39. The method of claim 38 wherein the coordinates of Table 5 comprise at least 2 atoms of the amino acid residues of Table 8.

40. A computer-based method of rational drug design comprising:

(a) providing the coordinates of at least two atoms of a P450 3A4 structure as defined in Table 5 ± a root mean square deviation from the Cα atoms of less than 1.5 Å ("selected coordinates");

(b) providing the structures of a plurality of molecular fragments;

(c) fitting the structure of each of the molecular fragments to the selected coordinates; and (d) assembling the molecular fragments into a single molecule to form a candidate modulator molecule.

41. The method of claim 40 further comprising the step of:

(a) obtaining or synthesising the molecular fragment or modulator molecule; and

(b) contacting the molecular fragment or modulator molecule with P450 3A4 to determine the ability of the molecular fragment or modulator molecule to interact with P450 3A4.

42. A method for identifying a candidate modulator of P450 3A4 comprising the steps of:

(a) employing a three-dimensional structure of P450 3A4, at least one sub-domain thereof, or a plurality of atoms thereof, to characterise at least one P450 3A4 binding cavity, the three-dimensional structure being defined by atomic coordinate data according to Table 5 ± a root mean square deviation from the Cα atoms of less than 1.5 Å; and

(b) identifying the candidate modulator by designing or selecting a compound for interaction with the binding cavity.

43. The method of claim 42 further comprising the step of:

(a) obtaining or synthesising the candidate modulator; and

(b) contacting the candidate modulator with P450 3A4 to determine the ability of the candidate modulator to interact with P450 3A4.

44. A method for determining the structure of a protein, which method comprises;

providing the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å or selected coordinates thereof, and

either (a) positioning said co-ordinates in the crystal unit cell of said protein so as to provide a structure for said protein, or (b) assigning NMR spectra peaks of said protein by manipulating said co-ordinates.

45. A method for determining the structure of a compound bound to P450 protein, said method comprising:

providing a crystal of P450 protein;

soaking the crystal with the compound to form a complex; and

determining the structure of the complex by employing the data of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å or a portion thereof.

46. A method for determining the structure of a compound bound to P450 protein, said method comprising:

mixing P450 protein with the compound;

crystallizing a P450 protein-compound complex; and

determining the structure of the complex by employing the data of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å or a portion thereof.

47. A method of obtaining a representation of the three dimensional structure of a crystal of cytochrome P450 3A4, which method comprises providing the data of Table 5 or selected coordinates thereof, and constructing a three-dimensional structure representing said coordinates.

48. A computer system, intended to generate structures and/or perform optimisation of compounds which interact with P450, P450 homologues or analogues, complexes of P450 with compounds, or complexes of P450 homologues or analogues with compounds, the system containing computer-readable data comprising one or more of:

(a) the structure factor data for P450 as shown in Table 3;

(b) atomic coordinate data obtainable by the method of claim 5, said data defining the three-dimensional structure of 3A4 P450 or at least selected coordinates thereof;

(c) atomic coordinate data of a target P450 protein generated by homology modelling of (b);

(d) atomic coordinate data of a target P450 protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 3;

(e) structure factor data derivable from the atomic coordinate data of (c) or (d); and

(f) atomic coordinate data of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å or selected coordinates thereof.

49. A computer system according to claim 48, wherein said atomic coordinate data is for at least one of the atoms provided by the residues Phe57, Phe108, Phe213, Phe215, Phe219, Phe220, Phe241 and Phe304.

50. A computer system according to claim 48, wherein said atomic coordinate data is for at least one of the atoms provided by the residues of Table 7.

51. A computer system according to claim 50, wherein said atomic coordinate data is for at least one of the atoms provided by the residues of Table 8.

52. A computer system according to claim 48 comprising:

(i) a computer-readable data storage medium comprising data storage material encoded with said computer-readable data;

(ii) a working memory for storing instructions for processing said computer-readable data; and

(iii) a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-readable data and thereby generating structures and/or performing rational drug design.

53. A computer system according to claim 52 further comprising a display coupled to said central-processing unit for displaying said structures.

54. A method of providing data for generating structures and/or performing optimisation of compounds which interact with P450, P450 homologues or analogues, complexes of P450 with compounds, or complexes of P450 homologues or analogues with compounds, the method comprising:

(i) establishing communication with a remote device containing computer-readable data comprising at least one of:

(a) the structure factor data for P450 as shown in Table 3;

(b) atomic coordinate data obtainable by the method of claim 5, said data defining the three-dimensional structure of P450, or selected coordinates of atoms of P450;

(c) atomic coordinate data of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å or selected coordinates thereof;

(d) atomic coordinate data of a target P450 homologue or analogue generated by homology modelling of the target based on the data (b);

(e) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 3; and

(f) structure factor data derivable from the atomic coordinate data of (d) or (e); and

(ii) receiving said computer-readable data from said remote device.

55. The method of claim 54 wherein said atomic coordinate data is that of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å or a selected portion thereof.

56. A computer-readable storage medium, comprising a data storage material encoded with computer readable data, the data comprising at least a selected portion of the three-dimensional coordinates of claim 5.

57. A computer-readable storage medium, comprising a data storage material encoded with computer readable data, wherein the data are defined by all or a portion of the structure coordinates of the P450 protein of Table 5 or a homologue of P450, wherein said homologue comprises backbone atoms that have a root mean square deviation from the backbone atoms of Table 5 of not more than 1.5 Å.

58. A computer-readable storage medium comprising a data storage material encoded with computer-readable data, wherein the data are defined by:

(a) the structure factor data for P450 as shown in Table 3;

(b) atomic coordinate data obtainable by the method of claim 5, said data defining the three-dimensional structure of 3A4 P450 or at least selected coordinates thereof;

(c) atomic coordinate data of a target P450 protein generated by homology modelling of the target based on the data of (b);

(d) atomic coordinate data of a target P450 protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 3;

(e) structure factor data derivable from the atomic coordinate data of (c) or (d); and

(f) atomic coordinate data of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å or a selected portion thereof.

59. A computer-readable storage medium comprising a data storage material encoded with a first set of computer-readable data comprising a Fourier transform of at least a portion of the structural coordinates for the P450 protein obtainable by the method of claim 5 or defined by the structure of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å or selected coordinates thereof; which data, when combined with a second set of machine readable data comprising an X-ray diffraction pattern of a molecule or molecular complex of unknown structure, using a machine programmed with the instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

60. The computer-readable storage medium of claim 59 wherein said first set of computer-readable data comprise a Fourier transform of at least a portion of the structural coordinates for the P450 protein of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å or selected coordinates thereof.

61. A crystal of P450 3A4.

62. The crystal of claim 61 in apo form.

63. A crystal of P450 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions.

64. The crystal of claim 61 wherein said 3A4 comprises the sequence of SEQ ID NO:2

65. A crystal of P450 3A4 protein having a resolution better than 3.1 Å.

66. A crystal of P450 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å.

67. A method of predicting three dimensional structures of P450 homologues or analogues of unknown structure, the method comprises the steps of:

aligning a representation of an amino acid sequence of a target P450 protein of unknown three-dimensional structure with the amino acid sequence of the P450 of Table 5 ± a root mean

square deviation from the Cα atoms of not more than 1.5 Å to match homologous regions of the amino acid sequences;

modelling the structure of the matched homologous regions of said target P450 of unknown structure on the corresponding regions of the P450 structure as defined by Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å; and

determining a conformation for said target P450 of unknown structure which substantially preserves the structure of said matched homologous regions.

68. The method of claim 67 wherein said target P450 protein is selected from the group consisting of 3A5, 3A7 or 3A43.

69. A chimaeric protein having a binding cavity which provides a substrate specificity substantially identical to that of P450 3A4 protein,

wherein the chimaeric protein binding cavity is lined by a plurality of atoms which correspond to selected P450 3A4 atoms lining the P450 3A4 binding cavity, the relative positions of said plurality of atoms corresponding to the relative positions, as defined by Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, of said selected P450 3A4 atoms.

70. A method of assessing the ability of a compound to interact with P450 3A4 protein which comprises:

obtaining or synthesising said compound;

forming a crystallised complex of a P450 3A4 protein and said compound, said complex diffracting X-rays for the determination of atomic coordinates of said complex to a resolution of better than 2.8 Å; and

analysing said complex by X-ray crystallography to determine the ability of said compound to interact with the P450 3A4 protein.

71. A method of preparing a composition comprising identifying a molecular structure or modulator according to the method of claim 40 or 42, and admixing the molecule with a carrier.

72. A process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a molecular structure or modulator according to the method as defined in claim 40 or 42; and (b) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

73. A process according to claim 72 which comprises (a) identifying a molecular structure or modulator according to the method as defined in any one of claims 28 to 40; (b) optimising the structure of the modulator molecule; and (c) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

74. A compound identified, produced or obtainable by the process or method of claim 40 or 42.

75. A compound of claim 74 or composition thereof for use in medicine.

76. A computer-based method for identifying a candidate modulator of P450 3A4 comprising the steps of:

employing a three-dimensional structure of P450 3A4, or selected co-ordinates thereof, the three-dimensional structure being defined by atomic coordinate data according to Table 5 $\pm$ a root mean square deviation from the Cα atoms of less than 1.5 Å; and

identifying the candidate modulator by designing or selecting a compound for interaction with the binding cavity.